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## **Trends in incidence of oesophageal and gastric cancer according to morphology and anatomical location, in Switzerland 1982-2011**

Feller, Anita ; Fehr, Martin ; Bordoni, Andrea ; Bouchardy, Christine ; Frick, Harald ; Mousavi, Mohsen  
; Steiner, Annik ; Arndt, Volker ; Clough-Gorr, Kerri M

**Abstract:** QUESTION UNDER STUDY/PRINCIPLES This study aimed to evaluate trends in the incidence of oesophageal and gastric cancer by anatomical location and histology using nationally representative Swiss data. **METHODS** We included all oesophageal and gastric cancers recorded in 10 Swiss population-based cancer registries 1982-2011. We calculated age-standardised incidence rates (ASIRs) per 100 000 person-years (PY) (European standard) for both cancer sites stratified by sex, language region (German, French-Italian), morphology and anatomical location. To assess time trends, we estimated annual percentage changes (APCs) with 95% confidence intervals (95% CIs). **RESULTS** ASIR of oesophageal adenocarcinoma increased in both sexes and language regions ( $p < 0.001$ ). The steepest increase occurred in males of the German-speaking region (APC 6.8%, 95% CI 5.8-7.8) with ASIRs of 0.8 per 100,000 PY in 1982-1987 and 3.9 per 100,000 PY in 2007-2011. Incidence of oesophageal squamous cell carcinoma decreased significantly in males of both language regions by around -1.5% per year. In contrast, a slight but significant increase (APC 1.4%, 95% CI 0.3-2.4) of oesophageal squamous cell carcinoma was observed in females of the German-speaking region. We observed stable rates for cancer of the gastric cardia. The incidence of noncardia gastric cancer decreased substantially in both sexes and language regions ( $p < 0.001$ ). **CONCLUSION** In Switzerland, the incidence of oesophageal adenocarcinoma has risen whereas incidence of noncardia gastric cancer has decreased substantially as observed in other developed countries.

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## Trends in incidence of oesophageal and gastric cancer according to morphology and anatomical location, in Switzerland 1982–2011

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### Summary

**QUESTION UNDER STUDY/PRINCIPLES:** This study aimed to evaluate trends in the incidence of oesophageal and gastric cancer by anatomical location and histology using nationally representative Swiss data.

**METHODS:** We included all oesophageal and gastric cancers recorded in 10 Swiss population-based cancer registries 1982–2011. We calculated age-standardised incidence rates (ASIRs) per 100 000 person-years (PY) (European standard) for both cancer sites stratified by sex, language region (German, French-Italian), morphology and anatomical location. To assess time trends, we estimated annual percentage changes (APCs) with 95% confidence intervals (95% CIs).

**RESULTS:** ASIR of oesophageal adenocarcinoma increased in both sexes and language regions ( $p < 0.001$ ). The steepest increase occurred in males of the German-speaking region (APC 6.8%, 95% CI 5.8–7.8) with ASIRs of 0.8 per 100,000 PY in 1982–1987 and 3.9 per 100,000 PY in 2007–2011. Incidence of oesophageal squamous cell carcinoma decreased significantly in males of both language regions by around –1.5% per year. In contrast, a slight but significant increase (APC 1.4%, 95% CI 0.3–2.4) of oesophageal squamous cell carcinoma was observed in females of the German-speaking region. We observed stable rates for cancer of the gastric cardia. The incidence of noncardia gastric cancer decreased substantially in both sexes and language regions ( $p < 0.001$ ).

**CONCLUSION:** In Switzerland, the incidence of oesophageal adenocarcinoma has risen whereas incidence of noncardia gastric cancer has decreased substantially as observed in other developed countries.

**Key words:** oesophageal cancer; gastric cancer; adenocarcinoma; squamous cell carcinoma; incidence; Switzerland

### Introduction

In Switzerland, each year approximately 500 new cases of oesophageal carcinoma are diagnosed and over 800 cases of gastric carcinoma. Owing to their high lethality, oesophageal and gastric cancers have a substantial public health impact in Switzerland [1, 2].

Studies in developed countries have reported substantial increases in the incidence of adenocarcinoma of the oeso-

#### Abbreviations

95% CI	95% confidence interval
APC	annual percentage change
ASIR	age-standardized incidence rates
BS/BL	Basel
FR	Fribourg
GE	Geneva
GR/GL	Glarus/Graubünden
JU/NE	Jura/Neuchâtel
PY	person-years
SG/AR/AI	Sankt Gallen/Appenzell Ausserhoden/Appenzell Innerhoden
TI	Ticino
US	United States
VD	Vaud
VS	Valais
ZH	Zurich

phagus and/or gastric cardia accompanied by stabilising or declining rates of oesophageal squamous cell carcinoma. In the United States (US), the incidence of oesophageal adenocarcinoma has risen rapidly since the mid-1970s, especially among white males, surpassing oesophageal squamous cell carcinoma [3]. During the same time period, the incidence of gastric cardia adenocarcinoma in the US also increased [3]. Similar trends have been observed in several European countries (e.g. the Nordic countries [4], Germany [5], Spain [6], United Kingdom [7–11]). However, there are substantial variations in both incidence rates and trends between countries and within regions [4, 12–15].

Data on the incidence of oesophageal adenocarcinoma in Switzerland have been mixed, were reported for varying timeframes and were regionally limited [4, 12, 13, 16–19]. An international study reported an increase in the incidence of oesophageal squamous cell carcinoma in women but no significant trends for oesophageal adenocarcinoma or cancer of the gastric cardia for Basel and Geneva (1973–1995) [4]. In other studies, no increase was found for the combined incidence rates of oesophageal and gastric cardia adenocarcinoma in Basel (1981–1992) [12] or for oesophageal adenocarcinoma in Eastern Switzerland (1989–1999) [17]. In contrast, increasing incidence of oesophageal adenocarcinoma has been reported for the canton of Vaud (1976–1994) [18], and for central Switzerland (1982–2007) [19].

This study aimed to evaluate trends in the incidence of oesophageal cancer (by both major histological subtypes and anatomical location) and gastric cancer (by anatomical location) using nationally representative data over a 30-year period.

## Methods

### Data sources

Data on primary oesophageal and gastric cancer diagnoses were obtained from Swiss cantonal cancer registries that held at least five years of consecutive data between 1982 and 2011. The study population included cases from Basel-Stadt/Basel-Landschaft (BS/BL), Fribourg (FR), Geneva (GE), Grison/Glarus (GR/GL), Neuchâtel/Jura (NE/JU), St. Gallen-Appenzell (SG/AR/AI), Ticino (TI), Valais (VS), Vaud (VD) and Zurich (ZH). The definition of primary cancers followed the rules defined by the International Association of Cancer Registries (IACR) and International Association for Research on Cancer (IARC) [20]. With the exception of cases from TI diagnosed prior to 2003, all cancer cases were coded according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3). Cases from TI diagnosed prior to 2003 were coded according to the second revision (ICD-O-2) and were automatically recoded to ICD-O-3 following international standards [21]. Proportions of death certificate only cases decreased from 4.9% in 1982 to 0.9% in 2011 (2.0% 1982–2011). In some cancer registries, a complete and systematic matching of registered incidence cases with data from death certificates was not carried out for all years [22]. The proportion of death certificate only cases with confirmed death certificate matching was 2.6% during

1982–2011. Overall, 94.3% of all cases were histologically verified ranging from 90.4% in 1982 to 95.6% in 2011. The Swiss Federal Statistical Office provided cantonal mid-year population estimates for all persons with permanent residence status within each canton.

## Classification by region

Switzerland has three major language regions (German, French, Italian) which adjoin countries sharing the same mother tongue. There are regional cultural differences between the language regions reflecting those of the countries bordering Switzerland. To enable a separate group inspection, we followed the approach of the Swiss Federal Statistical Office (SFO) and the National Institute for Cancer Epidemiology and Registration (NICER) and classified all cases into the following language regions: German-speaking (BS/BL, GR/GL, SG/AR/AI, ZH) and French-Italian-speaking (FR, GE, JU/NE, TI, VS, VD) [22, 23]. The language regions were formed by grouping the cantons according to the language spoken by the majority of the population. Overall, 85% of the permanent resident population of the cantons grouped to the German-speaking region indicated German as their main language. In the cantons of the French-Italian-speaking region, 68% of the population declared French and 17% Italian as their main language. Because of the gradual introduction of the cantonal cancer registries, the population covered by cancer registration in the French-Italian-speaking region ranged from 58.3% in 1982 to 100% since 2006. Coverage in the German-speaking region varied between 43.4% in 1982 and 46.9% in 2009. The coverage of the years 2010 and 2011 dropped to 38.9% because data from the cancer registry of BS/BL were not available at the time when the present statistical analysis was carried out.

### Classification by anatomical location and histology

Anatomical locations of oesophageal cancer were defined as: (1) upper and middle third (ICD-O-3: C15.0, C15.1, C15.3, C15.4), (2) lower third (ICD-O-3: C15.2, C15.5), and (3) overlapping / not otherwise specified (NOS) (ICD-O-3: C15.8, C15.9). Anatomical locations of gastric cancers were categorised into (1) cardia (ICD-O-3: C16.0), (2) noncardia and (3) overlapping/NOS (ICD-O-3: C16.8, C16.9). The proportion of NOS cases (ICD-O-3: Cx.9) varied substantially by cancer registry from 0.9% to 39.2% for oesophageal, and 11.2% to 26.9% for gastric cancer.

Histological categories were classified as: (1) adenocarcinoma (ICD-O-3: M814-M857), (2) squamous cell carcinoma (ICD-O-3: M8050-M8082), (3) other histology / NOS (ICD-O-3: M800-M804, M809-M813, M858-M994). Overall, proportions of cases with NOS histological subtypes (ICD-O-3: M800-M804) were 7.6% in oesophageal cancer and 6.4% in gastric cancer.

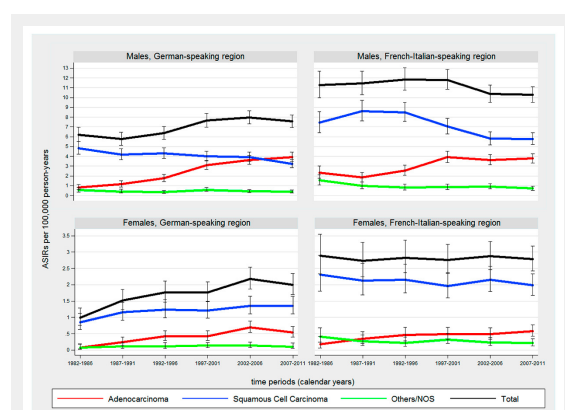
### Analytical methods

To assess time trends, annual and 5-year age-standardised incidence rates (ASIR; direct method, European standard [24]) per 100 000 person-years (PY) were calculated using mid-year population estimates for each canton. Estimated annual percentage changes (APC) with 95 percent confid-

ence intervals (95% CIs) were obtained by fitting linear regression models using the natural log of annual ASIRs as target variable and the year of incidence as predictor. Time trends were analysed by cancer site (oesophageal cancer, gastric cancer), histological subtype and anatomical location. Analyses stratified by anatomical location were restricted to cancer registries providing specified topography information for more than 80% of their cases (ICD-O-3: C15.0-C15.8, C16.0-C16.8), which led to exclusion of TI and ZH. All analyses were stratified by sex and language region.

## Results

Between 1982 and 2011, 7 280 oesophageal and 15 484 gastric cancers were diagnosed in the study population. The contributions of the regional cancer registries are shown in table 1. APCs for oesophageal and gastric cancers by sex, histology, anatomical location and language region are presented in table 2.



**Figure 1**

Time trends in age-standardised incidence rates (ASIRs) (European standard population) of oesophageal cancer by sex, histological subtype and language region from 1982 to 2011. NOS = not otherwise specified



**Figure 2**

Time trends in proportions of oesophageal cancer cases by sex, histologic subtype and language region from 1982 to 2011. ACC = adenocarcinoma; SCC = squamous cell carcinoma, Others/NOS = other histologic subtype / not otherwise specified

## Oesophageal cancer

For both sexes and all time periods under investigation, the incidence of oesophageal cancer was higher in the French-Italian-speaking region than the German-speaking region owing to distinctly higher rates of oesophageal squamous cell carcinoma ( $p < .001$  for all time periods). For example, the overall male ASIR in the French-Italian-speaking region ranged from 10.3–11.8 per 100 000 PY versus 5.8–8.0 per 100 000 PY in the German-speaking region. Overall, the incidence of oesophageal cancer was stable in the French-Italian-speaking region (male APC  $-0.5$  [95% CI  $-1.0, 0.0$ ], female APC  $-0.1$  [95% CI  $-0.7, 0.6$ ]), but increased in the German-speaking region (male APC  $1.2$  [95% CI  $0.6, 1.8$ ], female APC  $2.5$  [95% CI  $1.4, 3.5$ ]). Oesophageal cancer was much more frequent in males than in females (85% and 75% of oesophageal cancer occurring in males in the German and French-Italian regions, respectively). Squamous cell carcinoma represented more than 60% of all histological types of oesophageal cancer.

The incidence of oesophageal adenocarcinoma increased significantly in both sexes and language regions during 1982–2011. The steepest increase was observed in males of the German-speaking region (APC  $6.8\%$  [95% CI  $5.8, 7.8$ ]) with ASIRs of 0.8 per 100 000 PY in 1982–1987 and 3.9 per 100 000 PY in 2007–2011. In males of the French-Italian-speaking region, incidence of oesophageal adenocarcinoma rose substantially between 1987 and 2001 (APC  $6.7\%$  [95% CI  $4.3, 9.1$ ]) followed by a plateau of approximately 4.0 per 100 000 PY in subsequent years (fig. 1). In 2008–2011, both language regions showed similar ASIRs for oesophageal adenocarcinoma in both sexes ( $p > 0.05$ ). The male to female ratio for oesophageal adenocarcinoma was 10:1 in the German-speaking region and 6.5:1 in the French-Italian-speaking region for the latest time period.

The incidence of oesophageal squamous cell carcinoma decreased significantly in males of both language regions by around  $-1.5\%$  per year. In contrast, a slight but significant increase of oesophageal squamous cell carcinoma was observed in females of the German-speaking region with an ASIR of 0.8 per 100 000 PY in 1982–1987 and 1.4 per 100 000 PY in 2007–2011 (APC  $1.4\%$  [95% CI  $0.3, 2.4$ ]) (table 2, fig. 1). The male to female ratio of oesophageal squamous cell carcinoma was 2.4:1 in the German-speaking region and 2.9:1 in the French-Italian-speaking region. Squamous cell carcinoma was the predominant histological subtype of oesophageal cancer during the study period for females of both language regions and males of the French-Italian-speaking region. Overall, the proportion of oesophageal adenocarcinoma rose substantially from 1982–2011 and became the predominant histological subtype (53.8%) in males of the German-speaking region, surpassing squamous cell carcinoma in 2007–2011 (fig. 2).

Most cancers of the upper/middle oesophagus were squamous cell carcinomas (86.6%), whereas adenocarcinoma was the more common subtype of the lower part (48.1%). In males of both language regions, the increasing incidence trends of oesophageal adenocarcinoma were accompanied by an increase of cancers in the lower part of the oesophagus. However, in females this relationship was less clear (table 2).



### Gastric cancer

The German-speaking region showed significantly higher ASIRs of gastric cancer compared with the French-Italian-speaking region in 1982–1987 (1.2-fold higher in males and 1.4-fold higher in females,  $p < .001$ ), but more similar rates until the end of the observation period ( $p > 0.05$  in both sexes) (fig. 3). The incidence of gastric cancer decreased significantly in both sexes and language regions with APCs ranging from  $-1.5\%$  (95% CI  $-2.0$ ,  $-1.1$ ) in females of the French-Italian-speaking region to  $-3.2\%$  (95% CI  $-3.7$ ,  $-2.8$ ) in females of the German-speaking region. For cancer of the gastric cardia, no significant APCs were observed (table 2). The male to female ratio of cancer of the gastric cardia was 4.2:1 in the German-speaking region and 5.5:1 in the French-Italian-speaking region. The corresponding ratio for noncardia gastric cancer was 1.6:1 in both language regions. Cancer of the gastric cardia showed stable or slightly decreasing ASIRs ( $p > 0.05$ ) whereas the incidence of noncardia gastric cancer decreased significantly ( $p < 0.001$ ) in both sexes and language regions with APCs from  $-2.1\%$  (95% CI  $-2.9$ ,  $-1.3$ ) in females from the French-Italian-speaking region to  $-4.2\%$  (95% CI  $-5.0$ ,  $-3.3$ ) in males in German-speaking region. However, due to high proportions of NOS gastric cancer (13–20% per time period) these results should be interpreted with caution.

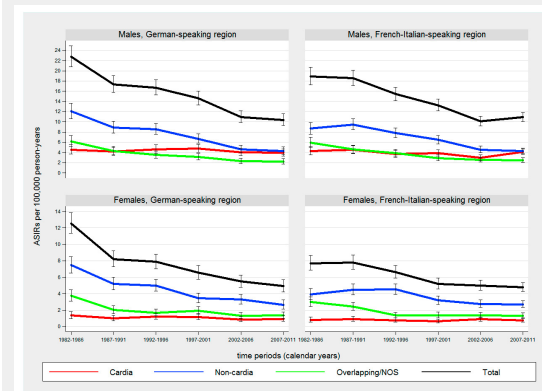
### Discussion

This study reports trends on oesophageal and gastric cancer incidence by location and histology in Switzerland from 1982 to 2011 by combining data from ten Swiss regional cancer registries.

We observed a substantial increase of oesophageal adenocarcinoma in Switzerland, as in other developed countries [3–11, 25–29]. In the German-speaking region of Switzerland, a continuous increase of oesophageal adenocarcinoma was observed throughout the study period, whereas a plateau was reached in males of the French-Italian-speaking region from 2001 onwards after a previous increase. In males of the German-speaking region oesophageal adenocarcinoma has become the predominant histology since

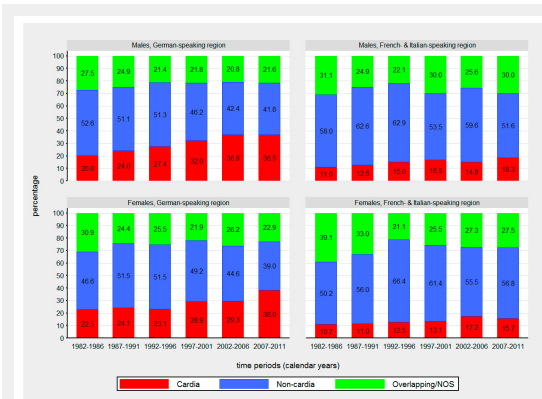
2007, accompanied by a corresponding decline of oesophageal squamous cell carcinoma.

Tobacco smoking and alcohol consumption have repeatedly been shown to be the major risk factors of oesophageal squamous cell carcinoma in developed countries, accounting for the large majority of all observed cases



**Figure 3**

Time trends in age-standardised incidence rates (ASIRs) (European standard population) of gastric cancer by sex, anatomical location and language region from 1982 to 2011. NOS = not otherwise specified



**Figure 4**

Time trends in proportions of gastric cancer cases by sex, anatomical location and language region from 1982 to 2011. NOS = not otherwise specified

**Table 1:** Oesophageal and gastric cancer cases in Swiss cancer registries from 1982 to 2011.

Cancer registry	Diagnosis period	Oesophageal cancer n (%)		Gastric cancer n (%)	
Basel Stadt / Basel Landschaft <sup>1</sup>	1982–2009	684	(9.4)	1 820	(11.8)
Fribourg <sup>2</sup>	2006–2011	117	(1.6)	140	(0.9)
Geneva <sup>2</sup>	1982–2011	866	(11.9)	1 424	(9.2)
Grisson/ Glarus <sup>1</sup>	1989–2011 1992–2011	285	(3.9)	696	(4.5)
Neuchâtel/ Jura <sup>2</sup>	1982–2011 2005–2011	356 38	(4.9) (0.5)	646 34	(4.2) (0.2)
St. Gallen–Appenzell <sup>1</sup>	1982–2011	725	(10.0)	2 096	(13.5)
Ticino <sup>2,3</sup>	1996–2011	383	(5.3)	1 009	(6.5)
Vaud <sup>2</sup>	1982–2011	1 644	(22.6)	2 036	(13.2)
Valais <sup>2</sup>	1989–2011	456	(6.3)	939	(6.1)
Zurich <sup>1,3</sup>	1982–2011	1 726	(23.7)	4 644	(30.0)

<sup>1</sup> German-speaking region

<sup>2</sup> French-Italian-speaking region

<sup>3</sup> Data from Zurich and Ticino were excluded for all analyses stratified by location (proportion of cases with unspecified location >20%).

[30–32]. As in other European countries, smoking-related cancers and smoking prevalence in Swiss males continues to decrease [33]. In addition, levels of alcohol consumption in Switzerland have been falling continuously in the last 30 years [34], especially among Swiss men [33]. However, alcohol consumption is distinctly more frequent in the French- and Italian-speaking region than in the German-speaking region and smoking prevalence is slightly higher in the French-speaking region compared with the German- and Italian-speaking regions of Switzerland [35]. Decreasing trends in male smoking prevalence and alcohol consumption are likely reflected in our results showing a substantial decline in squamous cell carcinoma of the oesophagus. Among Swiss women overall, increases in smoking prevalence have preceded substantial increases in lung cancer incidence (+16%) and mortality (+15%) (1998–2002 to 2003–2007) [36]. However, in this study an increasing trend of oesophageal squamous cell carcinoma was observed only in females of the German-speaking region.

Albeit less pronounced, tobacco smoking is also associated with an increased risk of adenocarcinoma of the oesophagus and gastric cardia [37, 38]. As previously mentioned, smoking prevalence in Swiss males continues to decline, which serves as an argument against smoking as a major contributing factor for the increase of oesophageal adeno-

carcinoma in Switzerland [36, 39]. The major factors discussed in the context of the rising incidence of oesophageal adenocarcinoma are increasing prevalence of gastro-oesophageal reflux disease (GORD) and obesity, and decreasing prevalence of *Helicobacter pylori* infection. Frequent symptoms of GORD have been shown to be associated with oesophageal adenocarcinoma. A 2010 meta-analysis reported a 5-fold increased risk of oesophageal adenocarcinoma among persons reporting at least weekly GORD symptoms and a 7-fold increase for those with daily symptoms, compared with individuals with less frequent or no symptoms [40]. A recent study reported an 11% increased risk of oesophageal adenocarcinoma for each 5 kg/m<sup>2</sup> increment of body mass index (BMI) [41]. Other studies suggest a synergistic interaction between BMI and GORD [42]. Based on a pooled analysis of data from the US, Australia and European countries, Hoyo et al. estimated that around 20% of oesophageal adenocarcinoma are attributable to synergistic effects of high BMI ( $\geq 27.5$  kg/m<sup>2</sup>) and the presence of GORD [42]. Like in other developed countries, an increasing prevalence of overweight and obesity has been observed in Switzerland. Between 1992 and 2012, the total overweight population (BMI  $\geq 25$  kg/m<sup>2</sup>) increased from 30.4% to 41.1% and in the obese segment (BMI  $\geq 30$  kg/m<sup>2</sup>) from 5.4% to 10.3% [33]. The prevalence of GORD in Swiss adults was 17.6% in 2004 [43]. The disease was

**Table 2:** Estimated annual percentage change for oesophageal and gastric cancer by sex, histology, anatomical location and language region from 1982 to 2011.

	German-speaking region				French-Italian-speaking region			
	n	APC	95% CI	p-value	n	APC	95% CI	p-value
<b>MALES</b>								
<b>Oesophageal cancers</b>	<b>2 564</b>	<b>1.2</b>	<b>0.6, 1.8</b>	<b>&lt;0.001</b>	<b>2 854</b>	<b>-0.5</b>	<b>-1.0, 0.0</b>	<b>0.058</b>
Location*								
Upper/middle third	463	-1.4	-2.6, -1.7	0.027	1 216	-0.6	-1.5, 0.2	0.136
Lower third	676	2.7	1.1, 4.3	0.002	1 073	0.8	0.1, 1.6	0.024
Overlapping/NOS	190	1.8	-0.4, -4.0	0.101	269	-2.8	-4.8, -0.8	0.008
Histology								
Adenocarcinoma	949	6.8	5.8, 7.8	<0.001	853	2.8	1.8, 3.8	<0.001
Squamous cell carcinoma	1 449	-1.4	-2.0, -0.7	<0.001	1 755	-1.5	-2.3, -0.8	<0.001
Others/NOS	166	-0.1	-2.2, 2.0	0.929	246	-2.4	-3.9, -0.8	0.004
<b>Gastric cancers</b>	<b>5 485</b>	<b>-3.1</b>	<b>-3.6, -2.8</b>	<b>&lt;0.001</b>	<b>3 763</b>	<b>-2.3</b>	<b>-2.9, -1.8</b>	<b>&lt;0.001</b>
Location*								
Cardia	775	-0.5	-1.3, 0.4	<0.258	893	-0.7	-1.9, 0.3	0.169
Noncardia	1 295	-4.2	-5.0, -3.3	<0.001	1 507	-3.4	-4.1, -2.6	<0.001
Overlapping/NOS	623	-4.3	-5.4, -3.3	<0.001	807	-3.7	-4.7, -2.7	<0.001
<b>FEMALES</b>								
<b>Oesophageal cancers</b>	<b>856</b>	<b>2.5</b>	<b>1.4, 3.5</b>	<b>&lt;0.001</b>	<b>1 006</b>	<b>-0.1</b>	<b>-0.7, 0.6</b>	<b>0.856</b>
Location*								
Upper/middle third	292	4.4	1.7, 7.1	0.002	524	0.2	-1.0, 1.4	0.719
Lower third	292	1.0	-1.0, 3.0	0.326	332	0.9	-0.4, 2.3	0.170
Overlapping/NOS	23	-0.9	-5.4, 3.4	0.647	53	-0.4	-3.4, 2.7	0.809
Histology								
Adenocarcinoma	235	5.5	3.3, 7.8	<0.001	183	4.1	2.6, 5.6	<0.001
Squamous cell carcinoma	553	1.4	0.3, 2.4	0.011	704	-0.5	-1.4, 0.3	0.219
Others/NOS	68	-1.6	-4.9, 1.7	0.315	119	-1.3	-3.7, 1.1	0.286
<b>Gastric cancers</b>	<b>3 771</b>	<b>-3.2</b>	<b>-3.7, -2.8</b>	<b>&lt;0.001</b>	<b>2 465</b>	<b>-1.5</b>	<b>-2.0, -1.1</b>	<b>&lt;0.001</b>
Location*								
Cardia	273	-1.5	-3.0, 0.1	0.065	267	0.0	-1.5, 1.4	0.962
Noncardia	1 124	-3.9	-4.8, -3.0	<0.001	1 163	-2.1	-2.9, -1.3	<0.001
Overlapping/NOS	522	-3.9	-5.5, -2.3	<0.001	582	-3.3	-4.8, -1.8	<0.001

95% CI = 95% confidence interval; APC = estimated annual percentage change; NOS = not otherwise specified

\* Data from Zurich and Ticino were excluded for all analyses stratified by location (proportion of cases with unspecified location >20%)

more frequent in the French-speaking region of Switzerland but equally distributed among the sexes. A meta-analysis of *H. pylori* infection, an important risk factor for noncardia gastric cancer [44, 45], showed a nearly 40% reduced risk of oesophageal adenocarcinoma in people infected with *H. pylori* [46]. Investigating the prevalence of *H. pylori* infection in Swiss adolescents in 1999–2002, Heuberger et al. found one of the lowest prevalence of *H. pylori* infection in Europe (9.7%) [47]. However, observed trends in known risk factors can only partly explain the rising incidence and the striking predominance of oesophageal adenocarcinoma in males [38].

For cancer of the gastric cardia, we observed stable rates in both sexes and language regions. Similar results have been reported from other developed countries (Australia 1982–1993 [26], Finland 1976–1995 [48], Netherlands 1973–2011 [49], Spain 1980–2004 [6]). In contrast, an increase of both oesophageal adenocarcinoma and cancer of the gastric cardia has been observed in Scotland (1978–1997) [7], eastern-England (1995–2006) [8] and the US (1974–1994) [3]. Since our analyses were based on data with high proportions of cases with unspecified anatomical location they should be interpreted with caution.

When adenocarcinomas of the (lower) oesophagus and gastric cardia have been examined, they have often been analysed together, on the assumption that both malignancies share several common features and have similar risk factors [50, 51]. However, substantial epidemiological differences between oesophageal and gastric adenocarcinoma have been described, suggesting that these two cancer sites may be distinct cancer types with partly different risk factors [52]. A recent review investigating risk factors for oesophageal and gastric cardia adenocarcinoma reported an association for GORD and oesophageal adenocarcinoma, but not for GORD and adenocarcinoma of the gastric cardia [53]. Furthermore, it remains unclear whether obesity is associated with an increased risk for adenocarcinoma of the gastric cardia, an established risk factor for oesophageal adenocarcinoma [53–55].

Similar to other developed countries, the incidence of noncardia gastric cancer decreased substantially in Switzerland [56]. The observed decline is presumably due to decreases in the prevalence of *H. pylori* infection, the main identified risk factor of noncardia gastric cancer [44, 45, 57]. In addition, reduction in the prevalence of tobacco smoking in males along with improvements in food preservation and nutrition may have also contributed to the decrease of noncardia gastric cancer incidence [57].

### Strengths and weaknesses

This is the first Swiss population-based investigation on oesophageal and gastric cancer trends providing the most nationwide representative findings to date. Although the cantonal cancer registries included do not cover the entire Swiss population, the large study sample representing the major language regions allows generalisability of these findings to the national level. Overall, the study population had less than 5% of death certificate only cases for each year under investigation indicating a high completeness of case ascertainment. Furthermore, the collection of cancer

cases showed a high proportion of histologically verified cases (>90% for each time period).

Population coverage of the German-speaking region was below 50% for all time periods under investigation. Therefore, incidence figures for the German-speaking region might be less precise than for the French-Italian speaking region. Another weakness of this study is the relatively large proportion of cancer cases with unspecified anatomical location. This was particularly true for gastric cancer, with approximately 16% of all analysed cases in this group. Because of high proportions of cases with unspecified location (>20%), cases from ZH and TI had been excluded for all analyses stratified by anatomical location. Population coverage for these analyses dropped by around 25% and 14% for the German-speaking region and French-Italian-speaking regions, respectively. Therefore these results should be interpreted with caution. Further, the formation of the language regions based on cantonal borders is just an approximation of the natural language regions of Switzerland. Some cantons are part of more than one language region. However, as cantonal information was the most detailed geographical information available, no more accurate allocation was possible within this work.

In Switzerland, healthcare and cancer registration is organised at the cantonal level (detailed descriptions of the Swiss health care system and the organisation of cancer registration can be found elsewhere [58–61]). Therefore it cannot be ruled out that regional differences in the provision of healthcare services and/or regional differences in the completeness of cancer registration might have influenced the results.

A major weakness of this study is the lack of information on prevalence trends in risk and protective factors covering the whole study period and/or periods preceding the observed incidence trends. Another limitation is the difficulty of distinguishing the organ of origin in cancers arising at the gastro-oesophageal junction [55, 62]. To circumvent this problem, several other studies have combined adenocarcinoma of the oesophagus and gastric cardia for their analyses. However, due to the high proportion of cases with unspecified anatomical location, this solution was not feasible for our study. Moreover, there is evidence that adenocarcinomas of the oesophagus and gastric cardia may be distinct cancer types, although they share some common risk factors [52, 53]. Last but not least, the rising incidence of oesophageal adenocarcinoma may be at least in part affected by an increase in the standard use of endoscopic procedures and advances in endoscopic technology, leading to more sensitive detection [63].

### Conclusions

In Switzerland the incidence of oesophageal adenocarcinoma has risen, whereas incidence of noncardia gastric cancer has substantially decreased during the study period 1982–2011. Reasons for the rising incidence in oesophageal adenocarcinoma may include increases in the prevalence of GORD and obesity. For oesophageal squamous cell carcinoma, mixed trends were observed, possibly related to sex and region-specific lifestyle changes. We observed stable rates for cancers of the gastric cardia. However, as



a result of high proportions of these cases with unspecified location, this finding should be interpreted with caution. Further investigations are needed to identify specific risk factors that may be responsible for the observed trends.

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## Figures (large format)

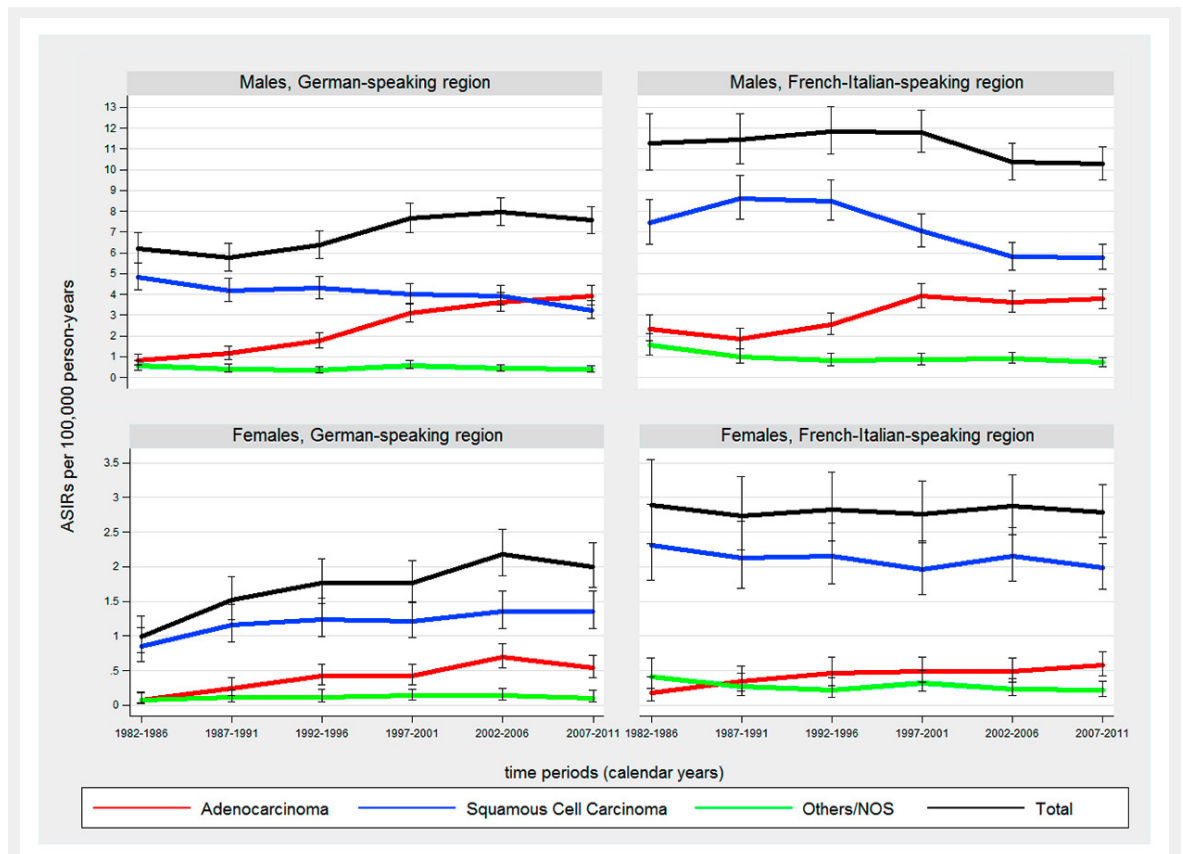
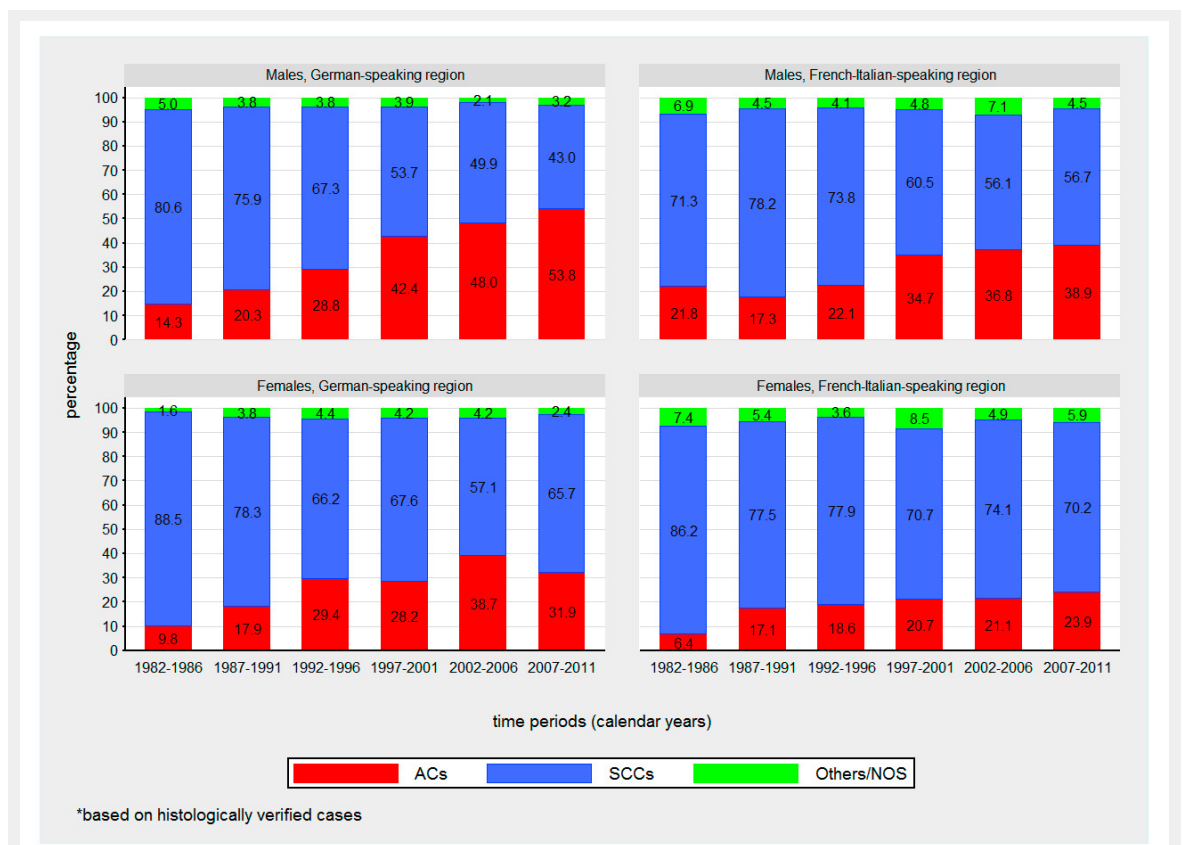


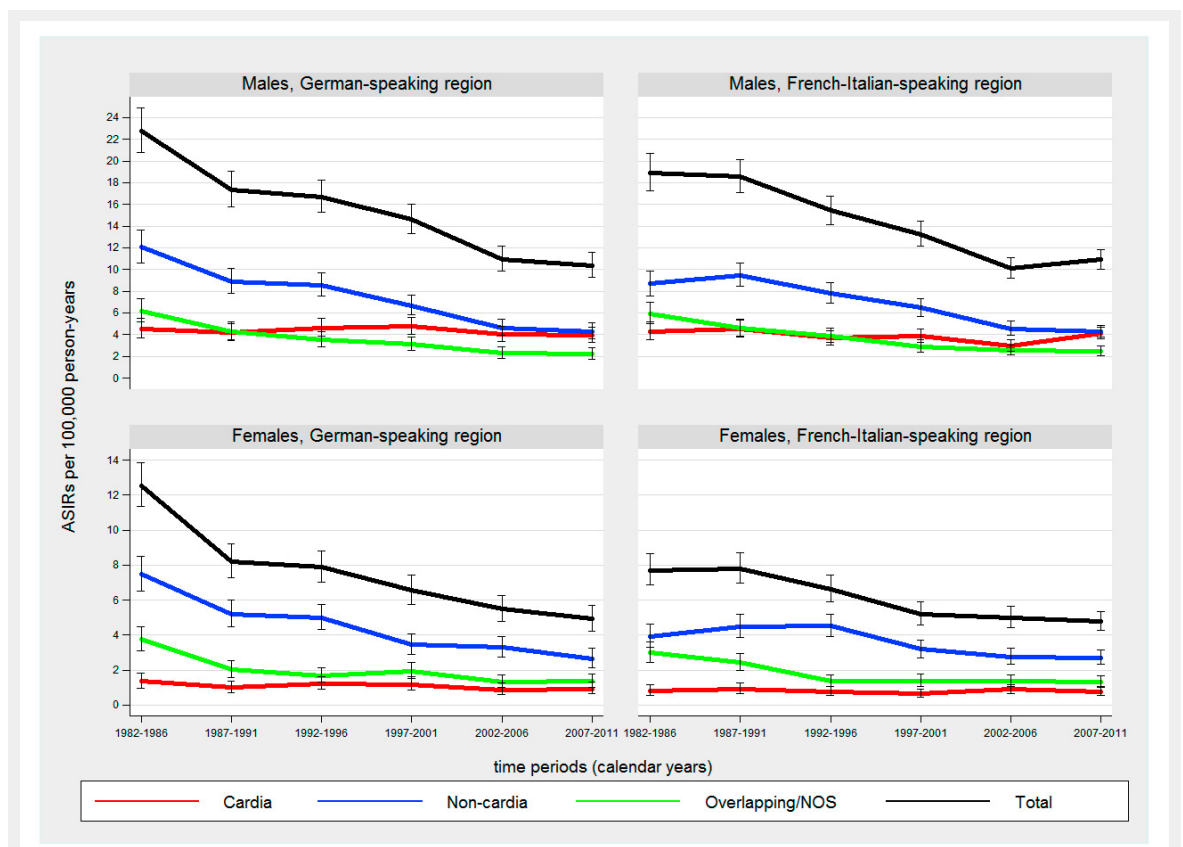
Figure 1

Time trends in age-standardised incidence rates (ASIRs) (European standard population) of oesophageal cancer by sex, histological subtype and language region from 1982 to 2011.

NOS = not otherwise specified

**Figure 2**

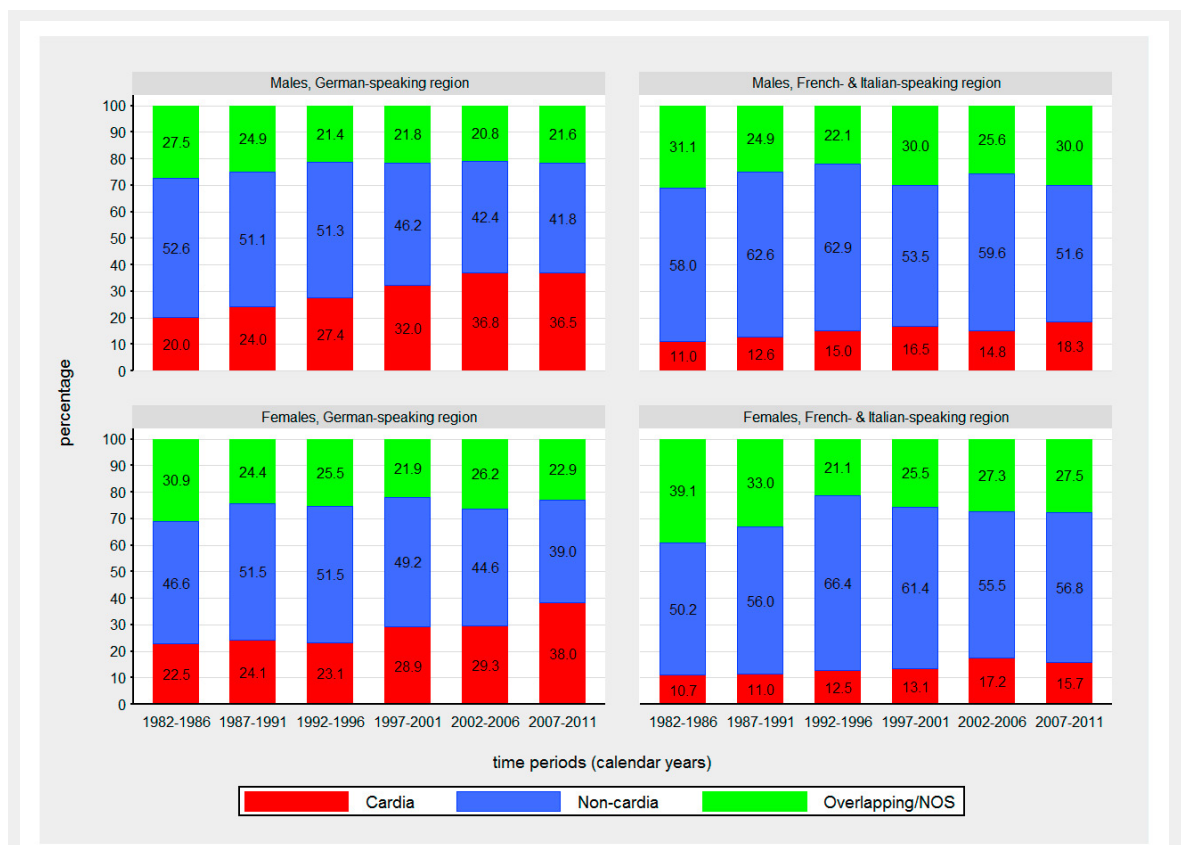
Time trends in proportions of oesophageal cancer cases by sex, histologic subtype and language region from 1982 to 2011. ACC = adenocarcinoma; SCC = squamous cell carcinoma, Others/NOS = other histologic subtype / not otherwise specified

**Figure 3**

Time trends in age-standardised incidence rates (ASIRs) (European standard population) of gastric cancer by sex, anatomical location and language region from 1982 to 2011.

NOS = not otherwise specified



**Figure 4**

Time trends in proportions of gastric cancer cases by sex, anatomical location and language region from 1982 to 2011.  
NOS = not otherwise specified